IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Richard M. Lawn, Gordon A. Vehar, and Karen L. Wion

Serial No.: 08/444,934

Group Art Unit: 1814

Filed: May 22, 1995

Examiner: Keith Hendricks

For: METHODS AND DEOXYRIBONUCLEIC ACID FOR THE PREPARATION OF TISSUE FACTOR PROTEIN

Assistant Commissioner for Patents
Washington, D.C. 20231

DECLARATION UNDER 37 C.F.R. § 1.132

Sir:

I, William Konigsberg, hereby declare that:

1. I am Professor of Molecular Biophysics and Biochemistry in the Yale School of Medicine at Yale University, and hold a Ph.D. in Chemistry from Columbia University and a B.S. in Chemistry from Rensselar Polytechnic Institute. I have been a faculty member at Yale University since 1964, and a full professor since 1968. I have over 35 years experience in the field of proteins, with an emphasis on blood proteins, and over 20 years experience in the study of tissue factor protein. This includes specific experience in cloning, manipulation, and expression of recombinant DNA encoding proteins, and specifically in the cloning, manipulation, and expression of recombinant DNA encoding human tissue factor. A partial curriculum vitae is attached to this declaration as an exhibit.

I have supervised, trained, observed, and communicated with numerous individuals working in the fields of proteins and the cloning and expression of genes in general and tissue factor in particular, including during the period 1985-1988. Based in part on this experience, I am familiar with what those of skill in the arts of proteins, cloning and expression, and tissue factor would understand when reading documents relating to proteins, cloning and expression, and tissue factor. Such documents are not interpreted by those of skill in this field in a vacuum, rather, such individuals bring to their reading an understanding of how to interpret such documents based on what has gone before and the conventions of the field.

2. I have reviewed the specification of the above-identified application, and the specification of Application Serial No. 07/013,743, filed February 12, 1987, to which the above-identified application claims priority.

3. I have reviewed the Office Action mailed January 17, 1996 in connection with the above-identified application.

4. I understand that claims 20-26 have been rejected under 35 U.S.C. § 112, first paragraph, as not being enabled by the specification. Specifically, I understand that the rejection is based on the contention that the description in the specification describing that the transmembrane region of human tissue factor can be deleted does not convey to those of skill in the art that such deletions can also include the deletion of the C-terminal amino acids (the "cytoplasmic" domain of tissue factor).

5. As an expert in the field of proteins in general and tissue factor in particular, and as an individual with extensive knowledge of the level of understanding of those of skill in the art of proteins, cloning and expression, and tissue factor at the time Application Serial No. 07/013,743 was filed, I believe that those of skill in the arts of proteins, cloning and expression, and tissue factor at that time would have understood the descriptions of deletion of the transmembrane region of tissue factor to include tissue factor proteins from which the entire C-terminal region, including the transmembrane and cytoplasmic regions, had been deleted. This is so because the deletion of the transmembrane region as described in the specification would have been viewed and understood as an indication that the extracellular domain could be used separately from both the transmembrane region and the cytoplasmic region. This can best be understood in terms of the overall structure of tissue factor as described in the specification. At the time, it was understood that transmembrane proteins generally functioned in one of two ways. In the first, the main activity of the protein resides in the extracellular domain, with the transmembrane domain serving to merely anchor the extracellular domain. In this scheme, the cytoplasmic domain is essentially irrelevant except for the first two basic residues which serve to help anchor the hydrophobic sequence that spans the membrane. In the second scheme, the transmembrane region serves as conduit for conducting signals between the extracellular domain and the cytoplasmic domain. Receptor proteins are (and were) a well-known example of this type of transmembrane protein. When a ligand binds to the extracellular domain of a receptor protein, this binding is communicated to the cytoplasmic domain via the transmembrane domain (thereby propagating an external

signal to the inside of the cell). From this scheme, it is clear, and those of skill in the art at the time would have understood, that deletion of the transmembrane region is equivalent to deletion of both the transmembrane region and the cytoplasmic region, since the cytoplasmic domain serves no purpose in the absence of the transmembrane domain. For these reasons, it is my opinion that those of skill in the art at the time the application was filed would have considered the reference to deletion of the transmembrane region to indicate that the inventors contemplated deletion of the C-terminal portion of tissue factor, including the cytoplasmic domain.

6. I declare that all statements made herein of my own knowledge and belief are true and that all statements made on information and belief are believed to be true, and further, that the statements are made with the knowledge that willful false statements are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: 7/16/96

William Konigsberg

CURRICULUM VITAE

Rev. 6/3/96

William H. Konigsberg, Ph.D.

BORN: April 5, 1930

EDUCATION:

Rensselaer Polytechnic Institutes, N.Y.	B.Sc.	1952	Chemistry
Columbia University, N.Y.	Ph.D.	1956	Organic Chemistry

CAREER:

1956 - 57	N.S.F. Fellow, The Rockefeller Institute.
1957 - 59	Research Associate, The Rockefeller Institute.
1959 - 64	Assistant Professor, The Rockefeller Institute.
1964 - 76	Associate Professor of Biochemistry, Yale University.
1976 - 84	Professor of Molecular Biophysics and Biochemistry, Yale University.
1984 - 87	Chairman, Department of Molecular Biophysics and Biochemistry, Yale University
1987 -	Professor of Molecular Biophysics and Biochemistry, Yale University.

PROFESSIONAL ACTIVITIES:

1968 - 72	Editorial Board: Archives of Biochemistry.
1969 - 73	Editorial Board: Biochem. Biophys. Acta.
1986 -	Editorial Board: Proteins: Structure, Function, and Genetics.

OTHERS:

American Chemical Society.
American Society of Biological Chemistry (Membership Committee), 1969 - 70.
National Institutes of Health, Biochemistry Study Section, 1970 - 74
National Institutes of Health, Physiological Chemistry Study Section, 1970 - 74.
U.S. - Israel Binational Science Foundation, 1974 - 84.
Minority Biomedical Review Council, 1976 - 86.
Advisory Council: Minority Career Opportunity Section, National Institutes of Health, 1976 - 86.

OTHERS cont.:

Ad Hoc consultant:
National Science Foundation
American Cancer Society
Heart and Lung Institute
Chairman: Gordon Conference on Proteins, 1976 - 77.
National Science Foundation Study Section, 1980 - 84.
American Society of Microbiologists, 1984 - present.

William H. Konigsberg

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Rev. 6/3/96